REMARKS

Upon entry of the present amendment, claims 36, 39-44, and 47-49 are pending in the application. The amendment to claims 36-39 is supported by disclosure at page 2, lines 11-16; page 6, lines 9-18; and page 23, lines 22-24, of the specification.

Informalities in the disclosure have been corrected as follows. The specification has been amended to clarify that HAAH polypeptide refers to the amino acid sequence of SEQ ID NO:2 and HAAH cDNA refers to the nucleotide sequence of SEQ ID NO:3. The claims have further been amended to insert sequence identifiers.

The specification was amended to add ATCC deposit information regarding antibody-producing hybridoma cell lines. A copy of the ATCC deposit receipt is enclosed (Attachment A)

No new matter has been added.

I. Claim Objections

Claims 39-43 were objected to as not complying with the 1.821(d) Sequence Rules and Regulations. The specification has been amended as described above to put the specification and claims in compliance with the Regulations.

II. Rejections under 35 U.S.C. § 112, second paragraph.

Claims 35, and 39-44 were rejected for indefiniteness.

With respect to claims 35 and 44, the Examiner stated

> [c]laims 35 and 44 are rendered vague and indefinite in the use of antibody designations 86A, 5C7, 19B, HA386A, HA15C7 and HA219B as the sole means of identifying the claimed antibodies and hybridoma cell lines.

Claims 35 was canceled, and claim 44 was amended to recited ATCC Accession Numbers.

Claims 39-43 were objected to because of the term "HAAH". The Examiner stated that amendment of the claim to incorporate SEQ ID NO:2 would overcome the rejection. Independent claim 39 was amended as suggested by the Examiner.

In view of these amendments, Applicants respectfully requested withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

III. Rejections under 35 U.S.C. § 112, first paragraph

Claims 35 and 44 were rejected for lack of enablement. Claim 35 was canceled, and claim 44 was amended to identify antibody-producing hybridoma cell lines, which were deposited with the ATCC. A copy of the ATCC deposit receipt is submitted herewith (Attachment A). Therefore, this rejection can now be withdrawn.

III. Rejections under 35 U.S.C. § 102

Claims 36-38 were rejected for anticipation by Radosevich et al. In the paragraph spanning pages 5-6 of Paper No. 17, The Examiner states

> Radosevich ('176) et al. (1985) discloses that the monoclonal antibody which reacts with a cell surface antigen on a human lung carcinoma cell line A549. Radosevich ('176) discloses that this antibody binds to an epitope from residues 117-123, which has an identical domain with HAAH (Fig. 3). Monoclonal antibody 44-3A6 would therefore cross-react with the instant SEQ ID NO:2. Recitation of the limitation of "polypeptides comprising the amino acid sequence of residues X-Y" does not limit the claims to antibodies which directly bind to the fragments recited. When given the broadest reasonable interpretation the claims are drawn to an antibody which binds any protein which minimally comprises the recited amino acid sequences.

As is well known in the art, the epitope binding site of a monoclonal antibody is a specific region (approximately 6-10 residues in length in the case of a linear peptide epitope) of an antigen to which that antibody binds. Recitation of an epitope binding site or binding specificity of a monoclonal antibody distinguishes that monoclonal antibody from other monoclonal antibodies

with a different epitope binding specificity. Claim 37-38 have been canceled, and claim 36 has been amended to require that the antibody be a monoclonal antibody that binds to SEQ ID NO:2 (HAAH) and with an epitope binding specificity containing residues 286-291 (double underlined) of SEQ ID NO:2.

Table 1 of the specification is reproduced below to more clearly define the epitope binding sites of the claimed monoclonal antibodies relative to those of the prior art.

Table 1: Amino acid sequence of HAAH

MAQRKNAKSS GNSSSSGSGS GSTSAGSSSP GARRETKHGG HKNGRKGGLS GTSFFTWFMV 61
IALLGVWTSV AVVWFDLVDY EEVLGKLGIY DADGDGDFDV DDAKVLLGLK ERSTSEPAVP 121
PEEAEPHTEP EEQVPVEAEP QNIEDEAKEQ IQSLLHEMVH AEHVEGEDLQ QEDGPTGEPQ 181
QEDDEFLMAT DVDDRFETLE PEVSHEETEH SYHVEETVSQ DCNQDMEEMM SEQENPDSSE 241
PVVEDERLHH DTDDVTYQVY EEQAVYEPLE NEGIEITEVT APPEDNPVED SQVIVEEVSI 301
FPVEEQQEVP PETNRKTDDP EQKAKVKKKK PKLLNKFDKT IKAELDAAEK LRKRGKIEEA 361
VNAFKELVRK YPQSPRARYG KAQCEDDLAE KRRSNEVLRG AIETYQEVAS LPDVPADLLK 421
LSLKRRSDRQ QFLGHMRGSL LTLQRLVQLF PNDTSLKNDL GVGYLLIGDN DNAKKVYEEV 481
LSVTPNDGFA KVHYGFILKA QNKIAESIPY LKEGIESGDP GTDDGRFYFH LGDAMQRVGN 541
KEAYKWYELG HKRGHFASVW QRSLYNVNGL KAQPWWTPKE TGYTELVKSL ERNWKLIRDE 601
GLAVMDKAKG LFLPEDENLR EKGDWSQFTL WQQGRRNENA CKGAPKTCTL LEKFPETTGC 661
RRGQIKYSI**M** **HPG**THVWPHT GPTNCRLRMH LGLVIPKEGC KIRCANETRT WEEGKVLIFD 721
DSFEHEVWQD ASSFRLIFIV DVWHPELTPQ QRRSLPAI (SEQ ID NO:2; GENBANK Accession No. S83325; His motif is underlined; conserved sequences within the catalytic domain are designated by bold type)

The labyrinthin protein described by Radosevich ('176) spans amino acids 59-312 of SEQ ID NO:2, with an amino acid difference at position 311. The epitope binding specificity of Radosevich's monoclonal antibody is PTGEPQQ, i.e., residues 117-123 of Labyrinthin, which correspond to residues 175-181 (bold underline) of SEQ ID NO:2. Since the epitope binding specificity of the claimed monoclonal antibody is completely different from that described by Radosevich ('176), Applicants request withdrawal of this rejection.

Claims 36-38 were also rejected for anticipation by Lavaissiere et al. In item 10, page 6, of Paper No. 17, the Examiner states

> Lavaissiere et al. teach a monospecific antiserum directed against the carboxyl terminal domain of bovine AAH, wherein said antiserum binds to human cells (citation omitted). Lavaissieret teach that in the carboxyl terminal catalytic domain, HAAH has 90% identity with bovine AAH (citation omitted). It is reasonable to conclude that this antiserum is

> binding to HAAH on human cells. Recitation of the limitation of "polypeptides comprising the amino acid sequence of residues X-Y" does not limit the claims to antibodies which directly bind to the fragments recited. When given the broadest reasonable interpretation the claims are drawn to an antibody which binds any protein which minimally comprises the recited amino acid sequences.

As is discussed above, the claims 37-38 have been canceled, and claim 36 was amended to require a monoclonal antibody that binds to HAAH (SEQ ID NO:2) and has a particular epitope binding specificity defined by residues 286-291 of SEQ ID NO:2. The claims as now amended exclude monoclonal antibodies that bind to any protein which minimally contain the recited sequences. Moreover, the cited reference fails to describe the required specific epitope binding site required by the claim.

> At the end of item 10 of Paper No. 17, the Examiner states,
>
> Further, the specification teaches on page 3, lines 11-13 that FB50 antibody binds to residues 286-291 of SEQ ID NO:2. The disclosure of Lavaissiere et al. would therefore anticipate claims drawn to an antibody or fragment thereof wherein said antibody binds to a polypeptide consisting of residues 286-291 of SEQ ID NO:2.

Lavaissiere et al. describe a monoclonal antibody called FB-50 that was used for immunoscreening and reports:

> A 636-bp cDNA clone was obtained after screening of a HPG2 γGT11 library with 125 FB-50 (mAb). The Hep G2-derived cDNA had a single major open reading frame (ORF) capable of encoding for a 212 amino acid protein, as illustrated in Fig. 4. The ORF had neither a methionine start codon nor a termination codon, but was in phase with the bacteriophage-derived lac Z gene reading frame, indicating that the epitope recognized by the FB-50 mAb derived from a linear amino acid sequence. (emphasis added; paragraph spanning pages 1316-1318 of Lavaissiere et al.)

As is well known in the antibody arts, a linear epitope is defined by a sequence about 6 to 10 adjacent amino acids that is recognized by an antibody. Fig. 4 and the accompanying figure legend provide additional information regarding the epitope binding specificity of Lavaissiere's antibody. The figure legend states: "The amino acid residues obtained by immunoscreening and

the corresponding FB-50 partial cDNA are underlined" (emphasis added). The underlined amino acids in Fig. 4 of Lavaissiere et al. correspond to residues 147-183 (dotted underline) of SEQ ID NO:2, indicating that the epitope recognized by Lavaissiere's antibody was located within that 147-183 residue linear sequence. In contrast, claim 36 requires a monoclonal antibody that has an epitope binding specificity of residues 286-291 of SEQ ID NO:2. The name of the antibody in the Lavaissiere et al. reference is irrelevant. Lavaissiere et al. fail to describe a monoclonal antibody with the epitope binding specificity required by the amended claims. Withdrawal of this rejection is respectfully requested.

Claims 36-38 were also rejected for anticipation by Carter et al. Carter et al. describe monoclonal antibodies and single chain antibodies, but also fail to describe a monoclonal antibody with the epitope binding site specificity required by amended claims 36. Therefore, this rejection should also be withdrawn.

IV. Rejections under 35 U.S.C. § 103

Claims 36-42 were rejected for obviousness over Radosevich et al. in view of Radosevich ('175) in view of Wels et al., Schlom and Goldenberg. On page 10, of Paper No. 17, the Examiner states:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the monoclonal antibody 44-3A6, or a single chain fragment therof for the monoclonal antibodies disclosed by Wels et al. in the method taught by Wels. It would further obvious to label said antibody and single chain antibody with a detectable label comprising a radioisotope, as taught by Schlom or a magnetic resonance imaging agent, Gd(III) or Fe(III) as taught by Goldenberg.

As is discussed above, Radosevich (Cancer Research article or '176 patent) fails to describe monoclonal antibodies with the HAAH epitope binding specificities required by the amended claims. Wels et al. does not describe any antibodies that bind to HAAH, much less the amino acid sequences of specific epitopes to which the antibodies bind. Schlom and Goldenberg also

fail to provide information regarding HAAH-specific antibody binding sites, but rather describe general antibody-based methods in diagnostic techniques. Therefore, claims 36, and 39-42 are nonobvious over this combination of references.

V. Double Patenting

Claims 35-39 were rejected for obviousness-type double patenting over claims of U.S. Patent Application No. 09/903,248 (the '248 application), which is a divisional patent application claiming priority to the parent of the present continuation-in-part application.

MPEP 804 outlines the requirements for establishing an obviousness-type double patenting rejection.

> In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent? If the answer is yes, then an "obviousness-type" nonstatutory double patenting rejection may be appropriate. Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 58 USPQ2d 1865 (Fed. Cir. 2001); Ex parte Davis, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000).

Claim 35 was rejected for obviousness-type double over claim 31 of the '248 application. Claim 35 has been canceled; therefore, this rejection is moot.

Claim 39 was rejected for obviousness-type double patenting of claims 34, 36, and 54-58 of the '248 patent application. The claims of the '248 patent application recite an antibody that binds to an epitope within the catalytic domain of HAAH (residues 650-700 of SEQ ID NO:2). Claim 39 has been amended to require an antibody with an epitope binding specificity of residues 286-291 of SEQ ID NO:2. The required epitope binding site is completely distinct, i.e., outside the domain recited or suggested by claims 34, 36, and 54-58 of the'248 patent application.

Therefore, issuance of the present claims would not unjustifiably extend the term of right to exclude of the claims of the '248 application, and this rejection should be withdrawn.

Claims 39-43 were rejected for obviousness-type double patenting over claims 34, 36, and 54-58 of the '248 patent application in view of Radosevich et al., Radosevich ('176 patent), Wels et al, Schlom and Goldenberg. The secondary references cited fail to change the interpretation of the claims of the'248 application or add any information that would suggest the specific epitope binding specificities required by the amended claims. Therefore, this ground of rejection should also be withdrawn.

Claims 36-38 were rejected for obviousness-type double patenting over claims 29, 42-44, 33-, 48-52, 39-41 and 45-47 of the '248 application. In support of this rejection, the Examiner stated that "recitation of the limitation 'polypeptides comprising the amino acid sequence of residues x-y does not limit the claims to antibodies which directly bind to the fragments suggested". As is discussed above, the claims were amended to define an epitope binding specificity, i.e., a short sequence to which a single monoclonal antibody binds. As is well known in the art, the epitope binding specificities of monoclonal antibodies can be fine mapped and defined with particularity. This amendment excludes antibodies that bind elsewhere, i.e., to an epitope defined by a different string of approximately 6-10 residues. The epitope binding specificities required by the amended claims are outside of the epitope binding region (residues 650-700 of SEQ ID NO:2) recited in the claims of the '248 application. Withdrawal of this rejection is therefore requested.

CONCLUSION

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

A petition for extension of time and a check in the amount of $950.00 is enclosed to cover the petition fee for a three-month extension of time pursuant to 37 C.F.R. § 1.17(a)(3). The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21486-032CIP.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

IABeattie

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Dated: December 19, 2003

TRA 1850752v1

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Rhode Island Hospital
Attn: Jack R. Wands, MD
Liver Research Center
55 Claverick Street, 4th Floor
Providence, RI 02903

Deposited on Behalf of: Rhode Island Hospital

Identification Reference by Depositor:	**Patent Deposit Designation**
Mouse hybridoma cell line: HA15C7A	PTA-3383
Mouse hybridoma cell line: HA219B	PTA-3384
Mouse hybridoma cell line: HA386A	PTA-3385
Mouse hybridoma cell line: FB501	PTA-3386

The deposits were accompanied by: __ a scientific description _ a proposed taxonomic description indicated above. The deposits were received May 17, 2001 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested May 30, 2001. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA

Signature of person having authority to represent ATCC:

Tanya Nunnally, Patent Specialist, Patent Depository **Date: June 27, 2001**

cc: Ingrid Beattie
(Ref. Docket or Case N .: 21486-032)